

Reexamination of the application of linear free energy relationships to the azaheterocyclic systems. III. Substituent effects on pK_a of five- and fused five- and six-membered ring systems

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The acid and basic pK_a values of purines are correlated according to both the Hammett and two-parameter Taft equations. The substituent effects on the basicity of imidazole and benzimidazole are also discussed in terms of these equations.

Кислотные и основные pK_a пуринов коррелированы по уравнению Гаммета и двух-параметрическому уравнению Тафта. Пользуясь этими уравнениями обсуждено также влияние заместителей на основность имидазола и бензимидазола.

Much attention has been paid to the problem of the substituent effects on the basicity of both the imidazole and benzimidazole systems. The pK_a — σ correlations have been successful [1—7]. On the other hand, the problem of both the protonation site and the substituent effects on pK_a in such very important system as purine remains unsolved.

The study of the substituent effects on the basicity of purine as well as of the ultraviolet absorption spectra of some its methyl and trifluoromethyl derivatives points to the N-1 atom to be the protonation site of that system [8]. The recent investigations involving ^{13}C —H satellite spectra of purine, however, have shown that the first proton is also shared between both the N-3 and N-7 atoms [9].

Qualitative observations [10] have led to conclusion that the substituent effects on the basicity of purine resemble those found for pyrimidine. However, this statement is not quite correct in our opinion. The substituent effects in the purine system have already been quantitatively studied but the magnitudes used for correlations are the 2-, 6-, and 8- proton chemical shifts [11] in the p.m.r. spectra of substituted purines. The correlations against σ and σ^+ have been successful and the effects operating are shown to be mainly of the mesomeric character [12].

We have plotted the pK_a^{20} values of several imidazoles, benzimidazoles, and purines (Tables 1 and 2) against σ as well as σ_I and σ_R according to eqns (1) and (2)

$$pK_a = \sigma \rho + \text{const} \quad (1)$$

$$pK_a = \sigma_I \rho_I + \sigma_R \rho_R + \text{const} \quad (2)$$

The results of the correlations are presented in Table 3.

On the basis of our recent results [13, 14], the following general rules can be derived. The ρ_I values close to -7.00 and below with simultaneous ρ_I/ρ_R ratio over 2.5 are typical of the correlations in the series bearing the substituents in the positions vicinal to the protonation site. The systems bearing the nitrogen atoms in

Table 1

Basic pK_{a,H_2O}^{20} of imidazoles and benzimidazoles

Compound	pK_a	Compound	pK_a
Imidazole	6.58*	Benzimidazole (contd)	
2-Me	7.75*	2-Ph	5.17*
2-Et	7.78*	2-CH ₂ OH	5.53**
2-Ph	6.30*	2-OEt	4.13** ^b
2-NH ₂	8.34*	5-Me	5.70*
2-NO ₂	-0.81*	5-NH ₂	5.97*
Benzimidazole	5.53	5-F	4.85** ^c
2-Me	6.11*	5-Cl	4.64*
2-Et	6.12	5-Br	4.56** ^c
2-NH ₂	7.54	5-CF ₃	4.17** ^c
		5-NO ₂	3.45*

Recalculated according to Perrin [15] from pK_a measured at various temperatures.

** This value is omitted due to strong deviation of the point from the correlation.

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Other values taken from [10].

Table 2

Basicities and acidities of purine and its derivatives [10]

Substituent	pK_a^a		Substituent	pK_a^a	
	basic	acidic		basic	acidic
None	2.39	8.93	6-NH ₂	4.25	9.83
2-NMe ₂	4.02	10.22	6-NHMe	4.18	9.99
2-NHMe	4.01	10.32	6-NMe ₂	3.87	10.5
2-NH ₂	3.80	9.93	6-OMe	2.21	9.16
2-OMe	2.44	9.20	8-NMe ₂	4.80	9.73
2-SMe	1.91	8.91	8-NHMe	4.78	9.56
2-Cl	0.69	8.21	8-NH ₂	4.68	9.36
6-Me	2.6	9.02	8-OMe	3.14	7.73
6-Cl	0.45	7.88	8-SMe	2.95	7.67
6-CF ₃	—	7.35	8-Me	2.85*	9.37
6-OEt	2.13	9.52	8-Cl	1.77	6.02
6-CN	0.3*	6.88	8-CF ₃	1.0	5.2
6-SMe	1.63	8.74	8-SO ₂ CH ₃	0.42	4.87

a) In water at 20°C. The possible experimental errors are within the range ± 0.05 units. This value is omitted because the point deviates from the correlation.

both 1- and 4-positions are exceptional in this respect. The effects of the substituents in the rings fused to that bearing the protonation site are characterized by ρ_1 which is mainly between -3.00 and -1.50 and rarely slightly below -3.00 . The ρ_1/ρ_R ratio varies and depends on whether the substituent is in the mesomeric position to the protonation site or in another one.

It can be seen that the correlations in the series of imidazoles and benzimidazoles follow these rules. Simultaneously, it may be seen that none of ρ_1 of the basic pK_a - σ correlations in the series of purines reaches -6.00 and the ρ_1/ρ_R ratio is always close to 2.00. It should also be mentioned that the correlations do not always cross the point corresponding to the pK_a of unsubstituted purine. Therefore, we assume that the position of the protonation site varies according to the pattern of substitution, even from one fused ring to another one, in such a way that the most favoured situation is created for the mesomeric effect to be operative. However, the latter never predominates.

The correlations of the acid pK_a values against various σ in the series of purines are also at least satisfactory. The vicinity of the 8-substituent and of the site of acid ionization results in a reduced role of the mesomeric interactions and in about two times more negative values of ρ and ρ_1 in comparison with those obtained in the correlations found for the 2- and 6-substituted purine series. Since the correlation

Table 3

pK_a^{20} — σ correlations in the series of imidazoles, benzimidazoles, and purines^a

Reaction series	ρ	ρ_1	ρ_R	ρ_1/ρ_R	$\frac{\rho_1}{\rho_1 + \rho_R} 100$	Intercept			
2- (M) Imidazoles	-8.74 ± 0.60	—	—	—	—	6.97 ± 0.11	0.423	0.991	6
	—	-7.73 ± 0.29	-3.08 ± 0.23	2.51	71.5	6.97 ± 0.07	0.179	0.999	6
2- (+M) Benzimidazoles	-10.79 ± 0.97	—	—	—	—	5.57 ± 0.11	0.226	0.981	7
	—	-9.68 ± 1.20	-4.01 ± 0.55	2.41	70.7	5.47 ± 0.15	0.306	0.971	7
5- (M) Benzimidazoles	-2.81 ± 0.20	—	—	—	—	5.56 ± 0.10	0.159	0.985	8
	—	-2.46 ± 0.17	-1.21 ± 0.12	2.03	67.9	5.43 ± 0.08	0.122	0.992	8
2- (+M) Purines ^c	-5.78 ± 0.20	—	—	—	—	2.82 ± 0.16	0.244	0.984	7
	—	-5.69 ± 1.03	-2.74 ± 0.55	2.08	67.1	2.64 ± 0.39	0.427	0.961	7
6- (+M) Purines ^c	-6.26 ± 0.70	—	—	—	—	2.75 ± 0.43	0.382	0.959	9
	—	-5.58 ± 0.47	-3.07 ± 0.26	1.81	64.5	2.21 ± 0.17	0.242	0.986	9
8- (+M) Purines ^c	-5.80 ± 0.29	—	—	—	—	3.78 ± 0.13	0.231	0.998	8
	—	-4.54 ± 0.35	-2.66 ± 0.15	1.76	63.0	3.10 ± 0.18	0.108	0.999	8
2- (+M) Purines ^f	-3.52 ± 0.26	—	—	—	—	9.51 ± 0.19	0.134	0.990	6
	—	-2.73 ± 0.58	-1.82 ± 0.34	1.50	60.0	8.97 ± 0.38	0.115	0.994	6
6- (+M) Purines ^f	-3.55 ± 0.34	—	—	—	—	9.61 ± 0.23	0.281	0.969	9
	—	-2.59 ± 0.54	-2.21 ± 0.40	1.17	54.0	8.72 ± 0.26	0.414	0.952	9
8- (+M) Purines ^f	-6.50 ± 0.39	—	—	—	—	8.42 ± 0.22	0.330	0.986	10
	—	-6.63 ± 0.54	-2.43 ± 0.28	2.72	75.0	8.50 ± 0.23	0.323	0.988	10

a) All correlations vs. σ_m ; b) standard deviations; c) correlation coefficient; d) number of the experimental points; e) for basic pK_a ; f) for acid pK_a .

lines also not always cross the point corresponding to unsubstituted purine the pattern of the substitution is assumed to influence the equilibrium between two forms bearing the acid ionization site at the 7- and 9-positions, respectively [16].

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